STATISTICAL ANALYSIS PLAN

Protocol Number and Title:	**A Long-term Follow-up Safety Study of Patients in the AVXS-101-CL-101 Gene Replacement Therapy Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101**
Protocol Version and Date:	**Amendment 4.0 / Protocol Version 3.0 / 05 Oct 2018**
Author(s):	**Haojun Ouyang, PhD** **Senior Biostatistician**
SAP Version:	1.0
SAP Version Date:	13-Nov-2018

REVISION HISTORY

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1.0	13-Nov-2018	Haojun Ouyang	SAP finalized

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Lead Biostatistician Haojun Ouyang Sr. Biostatistician	Date (dd-Mmm-yyyy)
Reviewing Biostatistician Sarah Kavanagh Biostatistician	Date (dd-Mmm-yyyy)
Francis Ogrinc, Ph.D. Sr. Director, Head of Biostatistics	Date (dd-Mmm-yyyy)
Olga Santiago, MD Chief Medical Officer	Date (dd-Mmm-yyyy)
Nancy Boman Sr. Vice President, Head of Regulatory Affairs	Date (dd-Mmm-yyyy)
Doug Feltner Vice President, Clinical Development	Date (dd-Mmm-yyyy)

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
AAV9	Adeno-associated virus serotype 9
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BLQ	Below Levels of Quantification
aCRF	Annotated Case Report Form
CRF/eCRF	Case Report Form/ electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
ICH	International Conference on Harmonization
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NA	Not Applicable
NCI	National Cancer Institute
PBMC	Peripheral Blood Mononuclear Cells
PCS	Potentially Clinically Significant
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SMN	Survival Motor Neuron
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TLF	Table, Listing and Figure
WHO	World Health Organization

1.1. Key Definitions

Term	Definition
AE	Adverse Event (AE): Any untoward medical occurrence in a clinical investigation patient. An AE does not necessarily have a causal relationship with the drug or device under study.
Age	For a given event, age will be expressed in years and rounded to one decimal place. Age at Study day 1 = ((Study day 1) visit date - date of birth + 1) / 365.25 and truncated to one decimal place. Age at annual visit = ((Date of annual visit) - date of birth + 1) / 365.25 and truncated to one decimal place.
Baseline	Baseline, unless otherwise specified in the Statistical Analysis Plan (SAP) sections, refers to the first visit of each patient who has enrolled in study AVXS-101-LT-001.

2. PURPOSE

The purpose of this document is to provide further details about the statistical analysis methods, data derivations and data summaries to be employed in the study protocol AVXS-101-LT-001: *A Long-term Follow-up Safety Study of Patients in the AVXS-101-CL-101 Gene Replacement Therapy Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101*.

This statistical analysis plan (SAP) is based on International Conference on Harmonization (ICH) E3 and E9 guidelines and in reference to protocol version 4.0: dated 05 Oct 2018 and Annotated Case Report Form (aCRF): dated 11 Sep 2018. The SAP covers statistical analysis, tabulations and listings of all data including effectiveness and safety data. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the Windows (Server 2008 R2) operating system.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified.

2.1. Responsibilities

AveXis, Inc. is responsible for ownership and approval of the SAP.

Syneos Health (CRO) is responsible for deriving the data sets according to CDISC standards and creating data set specifications based on the SAP. Syneos will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures.

2.2. Timings of Analyses

The safety and efficacy analysis will be conducted at such time that the last enrolled patient has completed the 10-year observational phase annual telephone contact; database lock will occur after all enrolled patients have completed the 10-year observational phase annual telephone contact or have discontinued study early. Syneos Health biostatistics will perform the analyses as described in Sections 7-11 of this SAP.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is:

- To evaluate long-term follow-up safety data of patients with spinal muscular atrophy (SMA) Type 1 who were treated with AVXS-101 in the AVXS-101-CL-101 gene replacement therapy clinical trial.

3.2. Exploratory Objective

The exploratory objective is to evaluate long-term developmental milestones achievement.

3.3. Statistical Hypotheses

Not applicable.

3.4. Study Design

In accord with National Institutes of Health (NIH) and Food and Drug Administration (FDA) Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events, this is a long-term, safety follow-up study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1 delivering AVXS-101. Patients will be asked to roll over from the previous study into this study for long-term safety monitoring. Patients will be enrolled in the study for 15 years of follow-up. The study will consist of an initial 5-year phase, during which subjects will be seen annually for evaluation of long-term safety and efficacy, followed by a 10-year observational phase.

The last visit of the parent study may serve as the visit at which the informed consent process is completed for this AVXS-101-LT-001 long-term safety study. Qualifying safety events occurring prior to entry in this study but after completion of the AVXS-101-CL-101 study will be captured in this study, after the informed consent process is complete. During the initial 5-year phase, patients will return to the investigative site for yearly follow-up study visits. If the patient is unable to visit the investigative site, the sponsor will arrange with the patients' local established physician to serve as an additional investigator to conduct the required assessments.

At each study visit, safety assessments will be conducted including:

- Medical history and record review;
- Physical examination including an assessment of ventilation and nutritional support (**Table 1**) and review of developmental milestones checklist (see **Table 6**);
    - New milestones demonstrated by patients which were not documented during the AVXS-101-CL-101 study must be supported by video evidence, obtained either during the course of the clinical visit or provided by parents/caregivers from home video.

- Height, weight, and vital sign measurements;
- Clinical laboratory evaluation;
- Pulmonary assessment;
- Cardiac assessment.

Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual study visits for review by the investigator.

Upon completion of the initial five years of follow-up visits, patients will be contacted via phone annually for the remaining 10-year follow-up period. During the 10-year observational phase, caregivers and patients will be contacted at least once a year and site staff will review a yearly questionnaire designed to elicit information regarding medical history, adverse events (AEs), and other clinical conditions. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual phone contacts for review by the investigator.

Throughout the 15-year study, the Investigator will maintain detailed patient records to include the following:

- Serious Adverse Events (SAEs) and hospitalizations
- Adverse Events of Special Interest (AESI)
- Exposures to SMA treatment clinical trial(s) or receipt of an investigational or approved product or therapy received with the intent to treat SMA
- Exposures to mutagenic agents and other medicinal products

The Investigator, patients and families, and other medical providers will report AEs, including unexpected illness and hospitalization.

Patients/families/caregivers will be instructed to report AEs and conditions directly to the investigative site. Caregivers will be instructed to record all AEs and SAEs, conditions, and medications and to make these available to the Investigator on an annual basis.

Study design is displayed in Figure 1.

Figure 1: Study Design

AVXS-101-CL-101 STUDY **AVXS-101-LT-001 STUDY**

AVXS-101 INFUSION	**AVXS-101-LT-001 ICF**	**15-YEAR LONG-TERM SAFETY FOLLOW-UP**	
Day –1 to 2	Last Study Visit or Early Discontinuation[a]	Initial 5-Year Phase Annual Safety Follow-up Study Visits	10-Year Observational Phase Annual Contact by Telephone and Questionnaire

[a] Last study visit or early discontinuation from the parent study is the visit at which the informed consent process maybe completed for the AVXS-101-LT-001 study

Table 1: Schedule of Assessments

	Initial 5-Year Follow-up Phase[a] Annual Study Visits						10-Year Observational Phase Annual Telephone Contact
Year	**0[b]**	**1**	**2**	**3**	**4**	**5**	**6-15**
Informed consent/assent[g]	X						
Inclusion/exclusion	X						
Demographic and medical history	X						
Review of medical history since previous visit		X	X	X	X	X	X
Gene therapy-related delayed adverse events, Serious adverse events, and other adverse events of interest	X	X	X	X	X	X	X
SMA treatments/mutagenic agents	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	
Height and weight	X	X	X	X	X	X	
Physical examination[e]	X	X	X	X	X	X	
Clinical laboratory assessments[f]	X	X	X	X	X	X	
Developmental milestone checklist	X	X	X	X	X	X	
Pulmonary assessments	X	X	X	X	X	X	X[h]
Telephone contact							X
Observational phase questionnaire[j]							X
24-Hour Holter Monitoring	X[i]	X	X	X	X	X	
12-lead electrocardiogram	X[i]	X	X	X	X	X	
Echocardiogram	X[i]	X	X	X	X	X	

a Study visits will take place annually (± 6 weeks). Patients will remain in the study for 15 years or until withdrawal.

b The last visit of the parent study or early discontinuation may be the timepoint at which the informed consent process is completed

c The End of Study visit will take place 15 years after the date on which the patient enrolled in the study.

d Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.

e Physical examination includes review of the following systems: head, ears, eyes, nose and throat; lungs/thorax; cardiovascular; abdomen; musculoskeletal; neurologic; dermatologic; lymphatic; and genitourinary. Assessment of ventilation and nutritional support and review of developmental milestones (through Year 5) will be reviewed and documented as part of the physical examination.

f Clinical laboratory assessments include hematology and blood chemistry.

g Informed assent process to be completed at the visit following the timepoint at which the subject reaches the age of assent, as per state legislation or institutional requirements of the investigative site. If during the 10–year observational period, assent will be completed via phone interview, as allowed per IRB guidelines/regulations.
h Pulmonary assessment during 10–year observational phase including only phone contact will include only patient-reported daily ventilatory support usage.
i Not required if done within 3 months of study entry.

3.4.1. Subject Selection

See section 8 in protocol for details.

3.4.2. Inclusion Criteria

See section 8 in protocol for details.

3.4.3. Exclusion Criteria

See section 8 in protocol for details.

3.4.4. Determination of Sample Size

Not applicable.

3.4.5. Treatment Assignment and Blinding

Not applicable.

3.4.6. Administration of Study Medication

Not applicable.

3.4.7. Study Procedures and Flowchart

Refer to **Table 1**.

4. ENDPOINTS

4.1. Safety Endpoints

The primary outcome for this clinical trial is safety. Safety assessments will be performed at the study visits annually during the first five (5) years.

4.1.1. Adverse Events

Serious AEs and Adverse Event of Special Interest (AESI) that occur from the start of enrollment of the AVXS-101-LT-001 trial through the last phone contact of the 10-Year Observational Phase will be collected and recorded in the eCRF. SAEs and AESI will be assessed for their seriousness, relatedness to study treatment, relationship to study discontinuation, and severity according to CTCAE version 4.03 criteria. AEs will be coded using the most current version of MedDRA available at the time the analysis is performed.

4.1.2. Laboratory Tests

Blood samples will be collected for hematology, including complete blood cell count (CBC) with differential and platelet with smear and clinical chemistry, at each annual visit.

4.1.3. Vital Signs, Body Weight and Length

Vital signs will be measured at each study visit through Year 5. Vital sign measurements will include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.

Height and weight will be measured at each visit through Year 5.

4.1.4. Physical Examination

A physical examination will be performed at each on-site visit through Year 5 and includes review of the following systems: head, ears, eyes, nose and throat; lungs/thorax; cardiovascular; abdomen; musculoskeletal; neurologic; dermatologic; lymphatic; and genitourinary. Evaluation of ventilation and nutritional support will be included as part of the physical examination as well as review of developmental milestones as per the Developmental Milestone Checklist (**Table 6**).

For any patients enrolled prior to amendment 3.0 which excluded completion of the developmental Milestone Checklist for patients opting to initiate an investigational or approved product or therapy received with the intent to treat SMA, an additional visit must be completed as soon as possible following IRB approval of protocol amendment 3.0 within the first year of the study to complete this assessment. If the milestone assessment was completed and documented as per standard of care at a previous office visit, this data can be captured in the eCRF and applicable videos can be collected once each applicable patient completes the informed consent form, as appropriate.

4.1.5. Pulmonary Examination

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit during the 5-year period requiring on-site visits.

During the study patients may be provided ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or investigator. Patients requiring non-invasive ventilatory support will be asked to summarize the hours per day usage in the month prior to the study visit.

During the 10-year observational period when patients are contacted annually via phone, the parent/legal guardian/patient will be asked to summarize the hours per day usage in the month prior to the study visit.

4.1.6. Echocardiogram

A standard transthoracic echocardiogram will be performed at study entry and annually through the Year 5 visit. An echocardiogram is not required if done within 3 months of study entry.

4.1.7. 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at study entry and annually through the Year 5 visit. A 12-lead electrocardiogram is not required if done within 3 months of study entry.

4.1.8. Holter monitoring

A Holter monitor will continuously record the patient's 12-lead ECG for a total of 24 hours at study entry and then annually through the Year 5 visit. Holter monitoring is not required if done within 3 months of study entry.

4.2. Efficacy Endpoints

The efficacy endpoints are developmental milestones based on the WHO-Multicentre Growth Study (WHO-MGRS) and the Bayley Scales of Infant and Toddler Development collected at each annual visit using "Development Milestone Checklist".

4.2.1. Developmental Milestones

In the case that a new developmental milestone is demonstrated during the physical examination (Section 4.1.3) for which the patient had not previously documented achievement in the AVXS-101-CL-101 study, video evidence will be captured either at the site or by collecting video from the parent(s)/legal guardian(s). Milestone achievement (**Table 6**) is defined as per the WHO-MGRS definitions [1] or Bayley Scales of Infant and Toddler Development, 3rd Ed. [2]; video documentation should demonstrate performance that satisfies the criteria for the specific item as defined by the relevant scale described in Developmental Milestone Checklist.

4.2.2. Video Evidence

AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

5. ANALYSIS SETS

5.1. All Enrolled Set

The All Enrolled Set will consist of all patients enrolled (i.e., completed the informed consent process) into the long-term follow-up LT-001 trial who completed the parent AVXS-101-CL-101 trial. Unless specified otherwise, this population will be used for patient listings and for summaries of patient disposition and for efficacy analysis.

5.2. Safety Set

All patients who enrolled in the AVXS-101-LT-001 trial will be included. For this study, the Safety Set will be the same as All Enrolled Set. The Safety Set will be used for all analyses of safety endpoints and for the presentation of patients in patient listings containing safety data.

5.3. Pharmacokinetic Set

Not applicable.

5.4. Pharmacodynamic Set

Not applicable.

5.5. Protocol Deviations

Protocol deviations identified by the site or the study monitor are to be reported to the Institutional Review Board (IRB) according to the IRB's reporting guidelines. All deviations are to be recorded in the electronic data capture database. They will be categorized in accordance with AveXis' Standard Operating Procedures (SOPs).

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. General Methods

In general, descriptive statistical methods will be used to summarize the data from this study. Continuous data, such as lab values, will be summarized using count, mean, median, standard deviation (SD), minimum, and maximum. For continuous data specified to be analyzed using parametric procedures, non-parametric procedures will be used if the parametric procedure is felt to be inappropriate.

Safety analyses will be conducted on the Safety Set. Efficacy analyses will be conducted on the All Enrolled Set. The efficacy summary table will be generated by year. All summaries will be produced by cohort (based on the cohort in study AVXS-101-CL-101) and overall.

All statistical analyses will be conducted with the SAS® software package version 9.3 or higher.

6.2. Missing Data

No imputation for missing data will take place for any efficacy or safety data collected. The follow rules will be used for date imputation

Table 2: Rules of Date Imputation

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day, but the year is present	The first date of the year.	The current visit date
Missing day, but year and month are present	First day of that month	Last day of that month
Missing month, but year and day are present	The first date of the year.	The current visit date

7. DERIVED AND TRANSFORMED DATA

7.1. Safety Variables

Any SAE or AESI reported as "Possibly Related", "Probably Related", or "Definitely Related" in the CRF will be consolidated and summarized as "Related". Any SAE or AESI reported as "Unlikely " or "Unrelated" will be consolidated and summarized as "Not Related".

7.2. Visit Windows

All time points and corresponding time windows are defined based on the end date of the patient's first visit.

For safety and efficacy analysis, the time windows specified in **Table 3** describe how data will be assigned to protocol-specified time points.

Table 3: Analysis Time Windows

Scheduled Visit	Nominal Days (Study Day)	Acceptable Analysis Window in Study Days (min day-max day)
Baseline (Year 0)	-	<1
Year 1	365	1 to 548
Year 2	730	549 to 913
Year 3	1095	914 to 1278
Year 4	1460	1279 to 1643
Year 5	1825	1644 to 2008

If multiple measurements are made on the same day for a safety laboratory parameter or a vital sign parameter, the average of the values will be used in analysis.

7.3. Pooling of Centers

Not applicable.

7.4. Subgroups

Not applicable.

8. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATIONS

8.1. Subject Disposition and Withdrawals

The number and percent of subjects in each analysis set will be tabulated by cohort and overall.

The number and percent of subjects who are still in the study, completed the study, and prematurely discontinued the study as of the time of reporting will be tabulated by cohort and overall.

Among those who prematurely discontinued the study, the distribution of reasons for discontinuation will be enumerated by cohort and overall.

A listing will be provided for all subjects who completed study AVXS-101-CL-101 and were unable to enroll in the AVXS-101-LT-001 study.

This analysis will be conducted on the All Enrolled Population.

8.2. Demographic and Other Baseline Characteristics

The age, weight, and height of the subject at the time of enrollment into AVXS-101-LT-001 and at each annual visit will be summarized by cohort and overall. The distribution of subjects by sex, ethnicity (Hispanic/Latino vs. Non-Hispanic/non-Latino), and race will be presented. Patient demographics will be summarized using the Safety Set.

Demographic data will be determined using the following calculations:

Age at Study day 1 = ((Study day 1) visit date - date of birth + 1) / 365.25 and truncated to one decimal place.

Age at annual visit = ((Date of annual visit) - date of birth + 1) / 365.25 and truncated to one decimal place.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

The presence of significant medical conditions obtained from medical history will summarized by cohort and overall using the All Enrolled Population. The following parameters will be summarized regarding symptoms and history of SMA: age at symptom onset, baseline SMA symptoms, family history of SMA, and number of siblings affected by SMA.

8.3. Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF by cohort and overall for the All Enrolled Population. The body systems will be presented in alphabetical order and the

conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with at least one condition/diagnosis will be summarized.

8.4. Prior and Concomitant Medications

Concomitant medications will not be captured; however, patients are encouraged to follow all routinely scheduled immunizations as recommended by the Center for Disease Control (CDC) or equivalent organization outside of the United States. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics.

Exposures to SMA treatment clinical trial(s) or receipt of an investigational or approved product or therapy received with the intent to treat SMA as well as mutagenic agents should be captured through Year 15. Mutagenic agents are defined as chemical including alkylating agents, crosslinking agents, and polycyclic aromatic hydrocarbons (PAHs) as well as physical agents such as ionizing radiation.

All concomitant medications, as specified above, will be classified using the ATC classification and preferred drug names from the WHO Drug Dictionary with the most current available version at the time the analysis is performed.

Prior and concomitant medications, as specified above, will be summarized separately by ATC level 2 and preferred drug name by cohort and overall for the Safety Set. A listing for prior and concomitant medications, as specified above, will also be provided.

9. SAFETY

Safety assessments will be performed at the study visits during the first five (5) years. Safety will be assessed based on SAE and AESI reports, clinical laboratory data, physical examinations, vital signs and pulmonary assessments.

Safety data will be summarized for each cohort and overall using the Safety Set.

9.1. Adverse Events / Adverse Drug Reactions

Adverse events will be coded using MedDRA. In study AVXS-101-LT-001, only SAEs (Section 9.2.1) or AESIs (Section 9.2.2) since the previous visit will be collected. The Investigator will document the SAE on the form provided and report the SAE as outlined in Section 12.4 of the protocol: Reporting Adverse Events.

9.2. Adverse Event Overview

An overview of AEs will be presented for each treatment cohort and overall for the Safety Set. The summary will consist of the number and percentage of subjects experiencing at least one event for the following AE categories:

- Any SAE, including the number and percentage of subjects with each SAE criteria met;
- Any AESI, including the number and percentage of subjects with each specific AESI reported
- Any SAE or AESI related to AVXS-101
- Any Grade 3 or 4 SAE or AESI
- Any Grade 3 or 4 SAE or AESI related to AVXS-101
- Any SAE or AESI leading to death

9.2.1. Serious Adverse Event

An SAE is an AE occurring during the study that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Any SAE that occurs after a patient has been enrolled, whether it is related to the study, must be recorded on forms provided by AveXis.

For all SAE summaries, the number of SAEs and the number and percentage of patients

experiencing SAEs will be tabulated according to System Organ Class (SOC) and Preferred Term (PT). Patients reporting more than one SAE for a given PT will be counted only once for that term, although each event will be counted individually. Patients reporting more than one SAE within an SOC will be counted only once for that SOC.

9.2.2. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician and may be reported to AveXis or designee if deemed necessary.

The identified AESI include:

- Gene-therapy related delayed AEs
- Liver Function Enzyme (LFE) elevations
- New malignancies
- New incidence or exacerbation of a preexisting neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of hematologic disorder

For all AESI summaries, the number of AESIs and the number and percentage of patients experiencing AESIs will be tabulated according to SOC and PT. Patients reporting more than one AESI for a given PT will be counted only once for that term, although each event will be counted individually. Patients reporting more than one AESI within an SOC will be counted only once for that SOC.

9.2.3. Adverse Events by PT

The number of SAEs/AESIs and the number and percentage of patients experiencing SAEs/AESIs will be summarized according to PT and sorted by overall frequency. Similar summaries will be provided for Grade 3 and Grade 4 SAEs and AESIs.

9.2.4. Adverse Events by Maximum Severity

SAEs and AESIs will be summarized by maximum CTCAE grade of each PT. Each PT will be assigned to a grade level, as assessed by the investigator, based on the CTCAE version 4.03 for grading severity of AEs. A patient who has an AE with unknown grade will be counted in the severity grade level category of "unknown". If the patient has another occurrence of the same event with a grade present, then the patient will be counted under the maximum grade that is present for the AE.

9.2.5. Adverse Events by Maximum Relationship

SAEs and AESIs will be summarized by maximum relationship of each PT to study product (AVXS-101), as assessed by the investigator. A patient who has an event with the assessment of 'Possibly Related', 'Probably Related' or 'Definitely Related' willbe summarized as 'Related' in the table. A patient who has an event with the assessment of 'Unrelated' will be summarized as 'Unrelated' in the table. If a patient has more than one occurrence of the same event, and one is 'related' and the other is 'unrelated', then the 'related' event is considered to be the one having the maximum relationship to study drug. If a patient has an AE with unknown relationship, then the patient will be counted in the relationship category of "unknown". The only exception is if the patient has another occurrence of the same AE with a relationship present. In this case, the patient will be counted under the maximum relationship category.

9.3. Laboratory Evaluations

9.3.1. Analysis of Laboratory Data

Blood data collected from EDC, including additional laboratory testing due to any SAEs, will be used in all analyses.

9.3.2. Variables and Criteria Defining Abnormality

Hematology variables include: hematocrit, hemoglobin, leukocytes, lymphocytes, Mean Platelet Volume (MPV), monocytes, neutrophils, platelets, bands, basophils, eosinophils

Ery. Mean Corpuscular HGB Concentration (MCHC), Ery. Mean Corpuscular Hemoglobin (MCH), Ery. Mean Corpuscular Volume (MCV), Erythrocytes (RBC), Erythrocytes Distribution Width (RDW).

Chemistry variables include: albumin, alanine aminotransferase (ALT/SGPT), alkaline phosphatase, amylase, aspartate aminotransferase (AST/SGOT), serum total bilirubin, carbon dioxide (CO2), chloride, creatinine, direct bilirubin, gamma glutamyl transferase (GGT), glucose, potassium, sodium, blood urea nitrogen, total creatine kinase, electrolytes.

The Criteria for Potentially Clinically Significant (PCS) Values will be based upon CTCAE Version 4.03 criteria (See Appendix 1) for Grade 2 or higher AEs unless otherwise specified.

9.4. Statistical Methods

Clinical laboratory tests at each annual visit will be summarized by the treatment cohort in study AVXS-101-CL-101 and overall. The baseline value will be the first visit of each patient in study AVXS-101-LT-001. Mean changes from baseline to each post-baseline visit (Year 1 to Year 5) will be summarized for each protocol-specified laboratory

parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, minimum, maximum, and median.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Shift tables from baseline to minimum value, maximum value, and Final Values will be created. The shift tables will cross tabulate the frequency of patients with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

The number and percentage of patients with post-baseline values meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in **APPENDIX 2** and **APPENDIX 3**) will be summarized by the actual treatment cohort and overall. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A listing will be provided that presents the entire set of lab values for the patients meeting PCS criteria during treatment.

For hemoglobin and the liver function tests (LFTs) of ALT, AST, alkaline phosphatase, and total bilirubin, the number and percentage of patients in each treatment group with a maximum CTCAE Grade of 1, 2, 3, or 4 at each visit during the initial 5-Year follow-up phase will be summarized. All LFT tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities. The hemoglobin table will include a summary row for the number and percentage of patients with at least a Grade 2 laboratory abnormality. Accompanying listings of all ALT, AST, total, indirect and direct bilirubin, and alkaline phosphatase will be created for any patients who had at least a Grade 3 ALT, AST, alkaline phosphatase, or total bilirubin. A listing of hematology results will be provided for subjects with hemoglobin abnormalities.

The number and percentage of patients meeting the following criteria will be summarized:

- ALT ≥3 × ULN and total bilirubin value ≥2 × ULN
- ALT ≥3 × ULN and total bilirubin value <2 × ULN;
- ALT >5 × ULN (equivalent to Grade 3 or higher) and total bilirubin value <2 × ULN;
- ALT <3 × ULN and total bilirubin ≥2 × ULN.

A patient or event will be counted if laboratory values meet the above criteria at any visit. The maximum ratio relative to the ULN will be used to determine if patients meet the criteria listed above. For patients meeting the ALT ≥3 × ULN and total bilirubin value ≥2 × ULN criterion, a corresponding listing of all ALT, AST, alkaline phosphatase, and total, direct, and indirect bilirubin values will be provided.

For patients meeting the criterion of ALT <3 × ULN and total bilirubin ≥2 × ULN, the number and percentage of patients with a total bilirubin value in the categories of ≤ULN, >ULN–<2 × ULN, and ≥2 × ULN at each annual visit will be summarized.

9.5. Vital Signs

Vital signs (pulse, respiration, temperature, diastolic blood pressure, body weight, systolic blood pressure, pulse oximetry) will be examined at each visit. Clinically-significant findings will be reported as an event only if determined to be a SAE or AESI.

A summary of changes from first recorded value in vital signs will be described at each visit by cohort and overall on the Safety Set. In addition, vital signs results will be flagged as PCS if they meet the pre-specified criteria outlined in **Table 4**. The number and percent of subjects meeting each PCS criterion will be summarized starting at Year 0 to Year 5.

Table 4: Criteria for Potentially Clinically Significant Vital Sign Values

Test / Measurement	Age	Low	High
Systolic blood pressure (mmHg)*	1-3 years	< 90	> 105
	3-6 years	< 95	> 110
	6-12 years	< 100	> 120
Diastolic blood pressure (mmHg)*	1-3 years	< 55	> 70
	3-6 years	< 60	> 75
	6-12 years	< 60	> 75
Pulse rate (beats/min)*	1-3 years	< 80	> 150
	3-6 years	< 70	> 120
	6-12 years	< 60	> 110
Body Weight**		Weight <3rd percentile for age and gender	Weight>97th percentile for age and gender
Temperature		<35°C	>39°C

* Adapted from Pediatric Advanced Life Support (PALS) Algorithm 2018

** Based upon National Health and Nutritional Determination Survey III Percentiles for age and gender

9.6. Physical Examination

Any abnormal findings on physical exam will be tracked as events only if determined to be SAE or AESI and will be listed by subject with the corresponding result on the baseline physical exam.

9.7. Pulmonary Examination

The pulmonary results will be provided in a listing.

Patients may be provided ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. The n, mean, median, range of number of hours per day of non-invasive ventilatory support will be summarized by visit and cohort and overall. At each annual visit and within cohort, the daily non-invasive ventilatory support use will be summarized based on patients' reports.

9.8. Echocardiogram

Echocardiograms will be conducted at Screening, every annual visit. Echocardiograms will be interpreted locally and results from the local interpretation (abnormal/normal, etc.) will be captured in the eCRF. Additionally, echocardiogram data will be provided to an external cardiologist for centralized review; this will be considered the primary echocardiogram source data.

Summaries of echocardiogram results (abnormal/normal, etc.) and findings (left ventricle function, patent foramen ovale, or other) based on the centralized review will be provided for all screening and post-baseline visits for each cohort. A listing of the local interpretation will also be provided.

9.9. ECG

A 12-lead ECG will be conducted at the scheduled visits in accordance with **Table 1**. ECGs will be interpreted locally by a cardiologist for immediate safety evaluation. The ECG tracings or ECG machine data will also be collected for centralized review and interpretation by a cardiologist.

Observed values as well as change from baseline values will be summarized at each scheduled visit using descriptive statistics for HR, PR, QR, QRS, QTcB, and QTcF as measured by the central reviewer.
In addition, ECG results will be flagged as PCS if they meet the pre-specified criteria outlined in **Table 5**. The number and percentage of patients meeting each PCS criterion at each scheduled visit and time point will be summarized. A listing of all PCS ECG values will be provided.

Table 5: Criteria for Potentially Clinically Significant ECG Values

Test / Measurement	Very Low (VL)	Very High (VH)
Heart rate (bpm)	<5th percentile for age	>95th percentile for age OR Change (increase) from baseline ≥20 bpm
QTcB (msec)	None	≥440 msec OR Change (increase) from baseline ≥30 msec
QTcF (msec)	None	≥440 msec OR Change (increase) from baseline ≥30 msec

9.10. Holter Monitoring

Patients will have a 12-lead continuous Holter monitor attached at Screening and every annual visit and the Holter will remain in place through 24 hours. Serial ECG data from Holter monitor will be pulled in at time points of '0 hour', '2 hour', '4 hour', '6 hour', '8 hour', '12 hour', '24 hour' and assessed by a central reviewer. The parameters, including HR, PR, QRS, and QTcF, will be measured by the central reviewer, at each time point. The summaries of Holter monitor data will be done by the actual treatment received overall and by dose and age group.

The central reviewer will identify abnormal ECGs that are potentially clinically significant (PCS), based on central reviewing guidelines provided by BMS. The number and percent of patients meeting each PCS criterion will be summarized starting at '2 hour' and continuing through '24 hour'.

10. EFFICACY

Efficacy analyses may be implemented as exploratory objective. The analysis of efficacy will be conducted using All Enrolled Set. Efficacy endpoints may be summarized separately for each cohort.

10.1. Efficacy Endpoint and Analysis

Efficacy measurements will be collected using the "Development Milestone Checklist" (**Table 6**) at each annual visit in the initial 5-Year Follow-up Phase.

The number and percentage of patients in the efficacy evaluable set at each annual visit who demonstrate the milestone of each item in the checklist will be summarized by cohort and overall. Also, a list of milestones each patient maintained or achieved will be provided. Those patients treated by other SMA treatments/mutagenic agents will be flagged.

Table 6: Development Milestone Checklist

Current Status: Achieved	Developmental Milestone: Bayley Scales of Infant and Toddler Development©[2]/WHO-MGRS[1]
YES/NO	Child holds head erect for at least 3 seconds without support[2]
YES/NO	Sitting with support[2]
YES/NO	Sitting without support[1]
YES/NO	Ability to crawl[1]
YES/NO	Pulls to stand[2]
YES/NO	Stand with assistance[1]
YES/NO	Stand alone[1]
YES/NO	Walk with assistance[1]
YES/NO	Walk alone[1]

10.2. Deviation from Analyses Planned in Protocol

Not applicable.

11. HEALTH ECONOMICS

Not applicable.

12. INTERIM ANALYSES

This is an open-label study, with a planned duration of 15 years, so it is likely that additional analyses will be conducted to summarize the findings at unspecified time points. Those analyses will follow this SAP as closely as possible.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

14. REFERENCE LIST

1. WHO Multicentre Growth Reference Study Group. WHO motor development summary: windows of achievement for six gross motor development milestones. Acta Paediatr. 2006;95 Suppl S450:86-95.

2. Bayley Scales of Infant and Toddler Development©, Gross Motor Subtest, item 19

3. Bonafide CP, Brady PW, Keren R, Conway PH, Marsolo K, Daymont C. Development of Heart and Respiratory Rate Percentile Curves for Hospitalized Children. Pediatrics. 2013 April; 131(4): e1150–e1157.

4. National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, Apr 2016.

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health standard SOPs provide an overview of the development of such SAS programs.

Syneos Health describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

For all data sets, tables and listings generated by SAS, Syneos Health Biostatistics will create SAS codes independently, and then use SAS PROC COMPARE procedure to perform 100% electronic comparison for all numerical and character values. In addition, the Lead Biostatistician, Lead Programmer and Senior Statistical Reviewer will review all Tables, Listings, and Figures (TLFs) for consistency and accuracy.

16. INDEX OF TABLES

Please refer to TLF Mock-ups.

17. INDEX OF FIGURES

Please refer to TLF Mock-ups.

18. INDEX OF LISTINGS

Please refer to TLF Mock-ups.

19. APPENDICES

APPENDIX 1: Definitions of CTCAE Grades 1, 2, 3, and 4

Lab Tests	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (decrease)			<8 -0 g/dL; <4.9 - 0 mmol/L; <80 -0 g/L	
Hemoglobin (increase)			> 4.0 above ULN or above baseline if baseline is above ULN	
White Blood Cells (decreased)	<LLN - 3000 x 10e6 /L; <LLN - 3.0 x 10e9 /L	<3000 - 2000x 10e6 /L; <3.0 - 2.0 x 10e9 /L	<2000 - 1000 x 10e6 /L; <2.0 - 1.0 x 10e9 /L	<1000 x 10e6 /L; <1.0 x 10e9 /L
White Blood Cells (increased)			>100,000 x 10e6 /L; > 100 x 10e9 /L	
Platelets	<LLN - 75,000 x 10e6/L; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000x 10e6/L; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000x 10e6/L; <50.0 - 25.0 x 10e9 /L	<25,000x 10e6/L; <25.0 x 10e9 /L
Absolute Neutrophils Count	<LLN - 1500x 10e6/L; <LLN - 1.5 x 10e9 /L	<1500 - 1000x 10e6/L; <1.5 - 1.0 x 10e9 /L	<1000 - 500x 10e6/L; <1.0 - 0.5 x 10e9 /L	<500x 10e6/L; <0.5 x 10e9 /L
Absolute Lymphocytes Count	<LLN - 800x 10e6/L; <LLN - 0.8 x 10e9 /L	<800 - 500x 10e6/L; <0.8 - 0.5 x 10e9 /L	<500 - 200x 10e6/L; <0.5 - 0.2 x 10e9 /L	<200x 10e6/L; <0.2 x 10e9 /L
AST	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Lab Tests	Grade 1	Grade 2	Grade 3	Grade 4
Gamma glutamyl transferase (GGT)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Total creatinine kinase	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
Serum total bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Glucose (decreased)	<LLN - 55 mg/dL; <ULN - 3 mmol/L	<55 - 40 mg/dL; <3 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Glucose (increased)	>ULN - 160 mg/dL; >ULN - 8.9 mmol/L	>160 - 250 mg/dL; >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L	>500 mg/dL; >27.8 mmol/L
Sodium (Increased)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L;
Sodium (decreased	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L;
Potassium (Increased)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L;	>7.0 mmol/L;
Potassium (decreased)	<LLN - 3.0 mmol/L		<3.0 - 2.5 mmol/L;	<2.5 mmol/L;
Albumin	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
Creatinine	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN

APPENDIX 2: Criteria for Potentially Clinically Significant Hematology Values

Test / Units	Age	Very Low (VL)	Very High (VH)
Hemoglobin (g/dL)	≥2Years - < 6Years	<10	>15.5
	≥6Years - <12 Years	<10	>17.5
	≥12 Years - <18 Years	<10	>18
Platelets Count (GI/L)	≥1 Year	<75	
White Blood Cell Count (GI/L)	≥1 Years - < 6 Years	<3.0	
	≥6 Years - ≤12 Years	<3.0	
Total Neutrophils (absolute, GI/L)	≥1 Year	<1.5	
Lymphocytes, Absolute (K/µL)	≥1 Year	<0.8	>4.1
Eosinophils (%)	≥1 Year		>5%

APPENDIX 3: Criteria for Potentially Clinically Significant Chemistry Values

Test / Units	Age	Very Low (VL)	Very High (VH)
Alkaline Phosphatase (U/L)	≥1 - <3 Years		>675
	≥3 - <13 Years		1037.5
ALT/SGPT	≤1-<3 Years		>150
	≥3 Years-<13Years		>144
AST/SGOT	≥1 Year - <3Years		>180
	≥3Years -64Years		>126
Total Bilirubin (mg/dL)	≥ 1 Year		>1.95
Creatinine (mg/dL)	>1 Year -<4Years		>1.5 X Baseline or >1.05
	≥4 Years - <7 Years		>1.5 X Baseline or >1.02
	≥7 Years - <10 Years		>1.5 X Baseline or >1.095
CK-MB	≥1 Year - <3 Years		>27
BUN (Urea Nitrogen) mg/dL	≥3 Years -<13 Years		>31.5

Test / Units	Age	Very Low (VL)	Very High (VH)
Fasting Glucose (mg/dL)	≥1 Year - <13 Years	<55	>160
Albumin (G/L)	≥1Year -<3Years	<30	
	≥1 - <3 Years	<30	
	3+ Years	<30	
GGT	≥1 Year - <3 Years		>300
	3 Years - 12 Years		>162.5
Potassium	≥1 Year - <3 Years	<3.8	>5.5
	≥3 Years - <13 Years	<3.5	>5.5
Sodium	0+ Years	< 135 mmol/L	>155mmol/L

20. REVISION HISTORY